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|---|
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| ART UNIT | PAPER NUMBER |
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| 1644 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/334,969 | Applicant(s) JAKOBSEN ET AL. | |
|---|---|---|---|
| | Examiner DiBrino Marianne | Art Unit 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12/9/02, 8/26/02, 4/12/02 & 7/20/01* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-11,14-27 and 34-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,14-27,34 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. Applicant's amendments filed 12/9/02 (Paper No. 22), 8/26/02 (Paper No. 20), 4/12/02 (Paper No. 18) and 7/20/01 (Paper No. 14) are acknowledged and have been entered.

Claims 1-11, 14-27 and 34-35 are pending.

2. Applicant is reminded of Applicant's election without traverse of Group I (claims 1-27), and species of the specific complex of a TCR tetramer comprising four αβ dimers and the specific linker molecule of avidin in Paper No. 7.

Claims 1-11, 14-27 and 34-35 read on the elected species and are presently being examined.

3. The abstract of the disclosure is objected to because: the abstract should appear as one paragraph. Correction is required. See MPEP § 608.01(b).

4. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

### Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.
(b) Cross-References to Related Applications.
(c) Statement Regarding Federally Sponsored Research or Development.
(d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).
(e) Background of the Invention.
    1. Field of the Invention.
    2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) Brief Summary of the Invention.
(g) Brief Description of the Several Views of the Drawing(s).
(h) Detailed Description of the Invention.
(I) Claim or Claims (commencing on a separate sheet).
(j) Abstract of the Disclosure (commencing on a separate sheet).
(k) Drawings.
(l) Sequence Listing (see 37 CFR 1.821-1.825).

5. Applicant is required to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, in the Brief Description of the Drawings, for the sequences appearing on page 57). See 37 C.F.R. 1.821(d).

6. The disclosure is objected to because of the following informalities:

No Brief Description of the Several Views of the Drawings has been disclosed in the specification.

Appropriate corrections are required.

**The following are new grounds of rejection necessitated by Applicant's amendments filed 12/9/02, 8/26/02, 4/12/02 and 7/20/01.**

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-11, 14-18 and 34-35 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 97/35991 (Applicant's IDS reference in the Form 1449 filed 1/31/00) in view of Golden et al (J. Immunol. Meth., Vol. 206: 163-169, 1997, Applicant's IDS reference in the Form 1449 filed 11/5/99), O'Shea et al (Science, Vol. 245: 646-648, 1989, Applicant's IDS reference in the Form 1449 filed 11/5/99), Garboczi et al (J. Immunology, Volume 157: 5403-5410, 1996, Applicant's IDS reference in the Form 1449 filed 11/5/99) and Schatz (Biotechnology, 11, 1993, pages 1138-1143, Applicant's IDS reference in the Form 1449 filed 11/5/99).

WO 97/35991 teaches soluble (i.e., extracellular domains) recombinant divalent and multivalent analogs (including tetravalent, i.e., a tetramer) of heterodimeric proteins and pharmaceutical compositions thereof, including αβ TCR that possess enhanced affinity for their target molecules, said αβ TCRs being associated via Ig linker molecules which may

further comprise a toxin, and/or may be further linked by association via avidin (especially page 8, line 31, page 9, lines 1-4, page 10, lines 27-31, page 11, lines 1-7, page 14, lines 7-16, Figure 1D and legend, claims 1-5, 8, 10-14, 17, 27 and 28, page 1, lines 14-17, page 16, lines 1-14). With regard to instant claim 17, the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims. In addition, WO 97/35991 teaches that the multimeric soluble TCR complexes may be useful in defining the specific peptide/MHC ligands recognized by uncharacterized tumor-specific T cells and T cells involved in autoimmune responses (especially page 10, lines 27-31 and page 11, line 1). WO 97/35991 also teaches production of the multimers in baculovirus with a yield of about 1 ug/ml (i.e., about 1 mg/L). WO 97/35991 also teaches short flexible Gly-Ser spacers between the TCR chain and the Ig portion (Figure 1D and legend).

WO 97/35991 does not teach multivalent soluble αβ TCR wherein each chain has a heterologous C-terminal dimerisation peptide which is a coiled coil domain (such as a leucine zipper from c-fos and c-jun) dimerization peptide, which dimerize, one with the other, and wherein a short flexible linker is between the TCR and the dimerisation domain, and further, wherein a disulfide bond present in the native TCR between the α and β chains adjacent to the cytoplasmic domain is absent from the recombinant TCR. WO 97/35991 does not teach the TCR complex of instant claims, wherein the disulfide bond between the α and β chain of the TCR are absent.

Golden et al teach soluble heterodimeric TCR comprising an α and a β chain, each chain comprising a leucine zipper which dimerizes, one with the other, produced in E. coli at yields of 4-5 mg/L (especially Abstract).

O'Shea et al teach heterodimer formation through leucine zippers from c-fos and c-jun (especially Abstract).

Garbozci et al teach a soluble TCR without the interchain disulfide bond present in native TCRs, and that the heterodimerization, refolding and antigenic specificity of the TCR do not require its interchain disulfide bond, transmembrane segments or glycosylation (especially Abstract and page 5408, column 1).

Schatz teaches a biotin holoenzyme synthetase encoded by birA, useful for labeling, purification, detection and immobilization of proteins. Schatz teaches fusion proteins comprising polypeptides and the birA sequence for biotinylation at a single specific site (especially abstract and last 2 paragraphs). Schatz teaches biotinylation of a variety of molecules is of practical importance, primarily due to the very tight binding of biotin to the proteins avidin and streptavidin, and that it is advantageous to accomplish biotinylation at a single site using an agent with site specificity (especially paragraph spanning columns 1 and 2 on page 1138).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have substituted the soluble heterodimeric TCR of Golden et al, with the Gly-Ser linker of WO 97/35991, as the monomeric TCR in the multimers of WO 97/35991 that were mulitmerized by avidin and to have produced the proteins in E. coli as taught by Golden et al. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made to have used any leucine zipper of appropriate stability such as the leucine zippers from c-fos and c-jun taught by O'Shea et al in the soluble heterodimeric TCR of Golden et al. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have to have a recombinant TCR as taught by the combination of WO 97/35991 and Golden et al without the disulfide bond, as taught by Garboczi et al and further modified as taught by Schatz.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to increase the yield of correctly folded soluble TCR of WO 97/35991 as modified with leucine zippers as taught by Golden et al and O'Shea et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do this because Garboczi et al teach that the presence of said bond is not important for heterodimerization and refolding, and further in order to facilitate the production of soluble correctly associated TCR, i.e., in order to insure that disulfide bonds did not form between homologous chains or with other contaminating proteins during purification.

With regard to instant claims 9 and 18, one of ordinary skill in the art at the time the invention was made would have been aware that biotin is the binding partner for avidin, and that biotin would have been incorporated into the monomer TCR in order that the monomer TCR could have been linked via avidin to form multimers and as taught by Schatz. With regard to instant claim 18, one of ordinary skill in the art at the time the invention was made would have been aware that the C-terminus of the heterodimer chain would be the optimal location for biotinylation, rather than at the N-terminus where preservation of antigen binding function was paramount.

Applicant's arguments in the amendment filed 7/20/01 have been fully considered, but are not persuasive.

It is Applicant's position (beginning on page 7 of the said amendment) that Golden et al teaches away from the claimed invention and that Barboczi et al teach the production of recombinant proteins which differ structurally from the claimed proteins for the reasons enunciated, briefly that Golden et al teach that elimination of the disulphide bond leads to loss of reactivity of confomationally-sensitive anti-TCR antibodies with the TCR $\alpha\beta$ constructs, that Garboczi et al teach TCR heterodimers which are present at non-physiologically relevant temperatures and high concentration, that the proteins of Garboczi et al differ structurally from the claimed proteins.

It is the Examiner's position that Golden et al teach reduction, i.e., elimination of both intrachain disulfide bonds as well as intra-chain disulfide bonds, the latter of which would be expected to disrupt the conformation of domains of TCR that would react to conformationally sensitive antibodies. It is the Examiner's further position that Garboczi et al teach both intra and inter chain disulfide bonds, that the heterodimerization and antigenic specificity of the TCR do not require its interchain disulfide bonds, and that Garboczi et al teach functional assays, i.e., physiologically relevant, with their TCR constructs. The claimed proteins comprise a recombinant αβ TCR wherein a disulfide bond present in native TCRs between the α and β chains adjacent to the cytoplasmic domain is absent.

9. Claims 1, 24 and 25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 97/35991 (Applicant's IDS reference in the Form 1449 filed 1/31/00) in view of Golden et al (J. Immunol. Meth., Vol. 206: 163-169, 1997, Applicant's IDS reference in the Form 1449 filed 11/5/99), O'Shea et al (Science, Vol. 245: 646-648, 1989, Applicant's IDS reference in the Form 1449 filed 11/5/99), Garboczi et al (J. Immunology, Volume 157: 5403-5410, 1996, Applicant's IDS reference in the Form 1449 filed 11/5/99) and Schatz (Biotechnology, 11, 1993, pages 1138-1143, Applicant's IDS reference in the Form 1449 filed 11/5/99) as applied to claims 1-11, 14-18 and 34-35 supra and further in view of U.S. Patent No. 5,635,363 (Applicant's IDS reference in Form 1449 filed 11/5/99).

WO 97/35991, Golden et al, O'Shea et al, Garboczi et al and Schatz (i.e., "the combined references") have been discussed supra. In addition, WO 97/35991 teaches that the multimeric soluble TCR complexes may be useful in defining the specific peptide/MHC ligands recognized by uncharacterized tumor-specific T cells and T cells involved in autoimmune responses (especially page 10, lines 27-31 and page 11, line 1).

The combined references do not teach a mutimeric TCR complex comprising a detectable label, nor attached to a "solid structure".

U.S. Patent No. 5,635,363 discloses soluble MHC/peptide tetramers which are biotinylated and multimerized with streptavidin or with avidin and which further comprise a light detectable label FITC or an enzyme (especially claims) and which further may be bound to an insoluble support such as a bead, i.e., a "solid structure", for the purpose of assay (especially column 8, lines 4-16).

It would have been prima facie obvious to one of ordinary skill at the time the invention was made to have biotinylated, as disclosed by the '363 patent for soluble MHC/peptide tetramers, the soluble TCR complexes taught by the combined references and to have multimerized them using avidin, and further to have labeled them with a detectable label such as is disclosed by the '363 patent for the MHC/peptide tetramers, or to have bound them to a bead, i.e., a solid structure.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to form more avid multimers because the combined references teach the claimed TCR complexes, WO 97/35991 teaches multimers and tetramers and both WO 97/35991 and the '363 patent teach use of avidin for multimerization of heterodimeric proteins, and also because one of ordinary skill in the art at the time the invention was made would have been motivated to facilitate detection because WO 97/35991 teaches that multimeric soluble TCR complexes may be useful in defining the specific peptide/MHC ligands recognized by uncharacterized tumor-specific T cells and T cells involved in autoimmune responses.

Applicant's arguments in the amendment filed 7/20/01 have been fully considered, but are not persuasive.

Applicant's arguments and Examiner's position supra with regard to item #8 of this Office Action, apply herein.

10. Claims 1 and 19-24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 97/35991 (Applicant's IDS reference in the Form 1449 filed 1/31/00) in view of Golden et al (J. Immunol. Meth., Vol. 206: 163-169, 1997, Applicant's IDS reference in the Form 1449 filed 11/5/99), O'Shea et al (Science, Vol. 245: 646-648, 1989, Applicant's IDS reference in the Form 1449 filed 11/5/99) and Garboczi et al (J. Immunology, Volume 157: 5403-5410, 1996, Applicant's IDS reference in the Form 1449 filed 11/5/99) and further in view of Ahmad et al (Cancer Res., Volume 53: 1484-1488, 1993).

WO 97/35991, Golden et al, O'Shea et al and Garboczi et al (i.e., "the combined references") have been discussed supra. The combined references do not teach a multimeric TCR complex attached to a lipid vescicle via derivatised lipid components of the vesicle.

Ahmad et al teach attachment of a biotinylated targeting antibody attached to the surface of a liposome containing biotinylated phosphatidylethanolamine by means of an avidin linker (especially Introduction and Liposome Preparation on page 1484). Ahmad et al further teach that liposomes containing lipid derivatives of polyethylene glycol have circulation times sufficiently long to allow for effective in vivo drug delivery.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have attached the multimeric TCR complex taught by the combined references to the liposome of Ahmad et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to effectively deliver in vivo the multimeric TCR complex taught by the combined references, including WO 97/35991 to be useful for in vivo therapy. Claim 23 is included in this rejection because it would also have been prima facie obvious to embed the TCR complex in the liposome of Ahmad et al because Ahmad et al teach effective delivery of a

substance embedded in the liposome rather than attached to the surface via a derivatized component of the liposome (especially Abstract). Instant claim 24 is included in this rejection because the claim limitation "solid structure" can read on "liposome" of the art reference.

Applicant's arguments and Examiner's position supra with regard to item #8 of this Office Action, apply herein.

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is 703-308-0061. The examiner can normally be reached on Monday and Thursday from 11 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on (703) 308-3973. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
March 20, 2003

PATRICK J. NOLAN, PH.D.
PRIMARY EXAMINER
3/24/03